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Real-time Interobserver Agreement in Bowel Ultrasonography for Diagnostic Assessment in Patients With Crohn's Disease: An International Multicenter Study

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Background: The unavailability of standardized parameters in bowel ultrasonography (US) commonly used in Crohn's disease (CD) and the shortage of skilled ultrasonographers are 2 limiting factors in the use of this imaging modality around the world. The aim of this study is to evaluate interobserver agreement among experienced sonographers in the evaluation of bowel US parameters in order to improve standardization in imaging reporting and interpretation.

Methods: Fifteen patients with an established diagnosis of CD underwent blinded bowel US performed by 6 experienced sonographers. Prior to the evaluation, the sonographers and clinical and radiological IBD experts met to formally define the US parameters. Interobserver agreement was tested with the Quatto method (*s*).

Results: All operators agreed on the presence/absence of CD lesions and distinguished absence of/mild activity or moderate/severe lesions in all patients. *S* values were moderate for bowel wall thickness ($s = 0.48$, P = n.s.), bowel wall pattern ($s = 0.41$, P = n.s.), vascularization ($s = 0.52$, P = n.s.), and presence of lymphnodes ($s = 0.61$, P = n.s.). Agreement was substantial for lesion location ($s = 0.68$, P = n.s.), fistula ($s = 0.74$, P = n.s.), phlegmon ($s = 0.78$, $P = 0.04$), and was almost perfect for abscess ($s = 0.95$, $P = 0.02$). Poor agreement was observed for mesenteric adipose tissue alteration, lesion extent, stenosis, and prestenotic dilation.

Conclusions: In this study, the majority of the US parameters used in CD showed moderate/substantial agreement. The development of shared US imaging interpretation patterns among sonographers will lead to improved comparability of US results among centers and

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facilitate the development of multicenter studies and the spread of bowel US training, thereby allowing a wider adoption of this useful technique.

Key Words: inflammatory bowel disease, radiology/imaging, Crohn's disease, inflammation

INTRODUCTION

The management of Crohn's disease (CD) has evolved over the last 2 decades; we have a better understanding of disease progression, and it has been established that there remains a disconnect between disease activity as defined by persistent inflammation and symptoms experienced by the patient. Unrecognized and uncontrolled inflammation can lead to progressive intestinal damage and complications requiring surgery. Therefore, improving access to monitoring strategies that are acceptable to patients, physicians, and society is important. Ideally, this would involve modalities that are safe, noninvasive, and readily accessible and can be delivered repeatedly at an acceptable cost, so that it can be integrated into close monitoring strategies. Bowel ultrasonography (US) represents an attractive first choice imaging modality in CD because it meets all the criteria mentioned. Bowel US can be repeated frequently for lesion assessment and monitoring over time. As bowel US does not involve radiation and has a low cost, it provides a convenient alternative to other radiological techniques, especially in children and young patients.[1–5]

Much like other imaging modalities, including magnetic resonance (MR) and computed tomography (CT), successful evaluation with bowel US depends on the acquisition of certain skills and experience, which may vary among individual operators. The current unavailability of standardized parameters in CD US and the shortage of skilled ultrasonographers are 2 limiting factors in the use of this imaging modality around the world. Interobserver agreement between operators with various degrees of experience in bowel US and its learning curve need to be investigated further.[6–9] Preliminary results from an Italian study showed that bowel US signs used in CD could be standardized with fair to good reproducibility among operators.[8] Hence the aim of this pilot study is to assess the interobserver agreement among bowel US experts from different centers, in the evaluation of established bowel US parameters commonly used in the diagnosis and monitoring of patients with CD.

METHODS

This prospective study was performed by 6 sonographers and 11 clinical and radiological experts from different inflammatory bowel disease (IBD) centers around the world (Canada, United States, Germany, Japan, Italy). The study was performed at Policlinico Universitario Tor Vergata in Rome during the meeting from July 16 to 18, 2015. The median time of practice in bowel US for the 6 operators was 20.5 years (range, 15–33 years), with more than 1000 exams per year. Prior to the evaluation of interobserver agreement, all the experts (sonographers, clinical and radiological experts) attended a 1-day meeting to formally define the US signs included in the study and the clinical relevance of all parameters (Table 1), using both videos and bowel US images. All of these US parameters have been previously described.[10–12]

Patients

Fifteen consecutive patients with established CD were enrolled based on accepted diagnostic criteria[13] of clinical, radiologic, endoscopic, and histologic findings. Clinical characteristics of patients are shown in Table 2. Patients were regularly

TABLE 1: US Parameters Selected and Standardized by the Experts

Bowel wall thickening	n.v. <3 mm for small bowel for at least 4 cm (<4 mm for colon)
Bowel wall pattern	Stratification conserved or disrupted
Stenosis	Coexistence of a thickened and stiff bowel loop with the loss of wall layers and severe lumen narrowing, with or without prestenotic bowel dilatation (>25 mm)
Fistula	Hypoechoic track with or without hyperechoic content seen outside the bowel loop, between loops, or between the loop and the urinary bladder
Phlegmon	*Hypoechoic mass with poor margination within the inflamed echogenic perienteri fat*
Abscess	Roundish anechoic lesions, with an irregular wall, often presenting internal echoes and posterior echo enhancement
Lymph node	Presence and short axis diameter >5 mm
Mesenteric adipose tissue alteration	Homogenous hyperechoic tissue surrounding thickened bowel walls observed in transverse section or easily detected when thickening of the hyperechoic halo of mesenteric fat around the bowel wall was consistently greater than the thickening of the normal bowel wall
Vascularization	*Vascularity within the thickened bowel wall evaluated by power-Doppler*

Abbreviation: n.v. = normal value.

TABLE 2: Clinical Characteristics of the 15 CD Patients

Sex, M/F	8/7
Median age (range), y	41 (20–64)
Smoking habits, No.	
Yes	10
No	5
Median time from diagnosis (range), mo	132 (7–235)
Montreal Classification, No. (%)	
Age at diagnosis	A1: 4 (26.7)
	A2: 8 (53.3)
	A3: 3 (20)
CD location	L1: 10 (66.7)
	L2: 0 (0)
	L3: 5 (33.3)
	L4: 0 (0)
CD behavior	B1: 1 (6.7)
	B2: 10 (66.7)
	B3: 4 (26.6)
Previous surgery, No.	
Yes	5
No	10
Previous exposure to anti-TNFs, No. (%)	6 (40)
Median CDAI at enrollment (range)	110 (50–310)
Median CRP level at enrollment (range), mg/L	5 (1–47)
Therapy at enrollment, No.	
Mesalamine	4
Corticosteroids	3
Thiopurines	2
Infliximab	2
Adalimumab	3
Corticosteroids + adalimumab	1

Abbreviations: anti-TNF = anti–tumor necrosis factor; CDAI = Crohn's Disease Activity Index; CRP, C-reactive protein.

followed up at the IBD Unit of Policlinico Universitario Tor Vergata of Rome, Italy. All patients underwent CD assessment (ileocolonoscopy and/or MR-enterography or CT-enterography) within 12 months before the study. At enrollment, 5 out of 15 patients had mild-moderate clinical activity (Crohn's Disease Activity Index [CDAI] > 150), and 1 patient was admitted to our Gastroenterology Unit after ultrasonographic assessment due to presence of an abdominal abscess confirmed by CT. Eligible patients were aged 18 years or older and were able to give written informed consent. Pregnant women and patients with a body mass index higher than 30 were excluded. Informed consent was obtained from all patients. This pilot study was approved by our institutional ethics committee (number 93.2015).

Diagnostic Evaluation

Recruited patients underwent 6 bowel US performed by the 6 operators, who were blinded to all other observations in the same day. The operators were not blinded to the clinical, endoscopic, and other imaging modality characteristics of patients. In all recruited patients, a Case Report Form was generated for bowel US parameters by each operator. For the purposes of data recording, bowel wall thickening (BWT; 3–7 mm vs >7 mm) (Fig. 1) and bowel wall pattern (preserved vs disrupted echostratification), were recorded, and measurements were considered for each segment of the bowel including the duodenum, jejunum, ileum, terminal ileum, and colon (rectum, sigmoid, descending colon, transverse, ascending, and cecum). For each segment, operators indicated the presence or absence of CD, the length of the disease, the presence of complications including stenoses with or without prestenotic dilation (Fig. 2), and extra-enteric complications such as abscess, phlegmon, or fistulae and/or lymph nodes or mesenteric adipose tissue alteration, and vascularization (absent/mild vs moderate/severe) (Fig. 3) was also recorded. All distinct sections of disease in each segment were recorded individually.

Bowel US was performed using the same ultrasonographic equipment (MyLabTwice, Esaote, Genoa, Italy). A first evaluation of the bowel was made with a convex transducer (frequency 1–8 MHz), followed by a high-frequency linear-array transducer (3–11 MHz). All patients fasted for 8 hours. Patients were positioned supine, bowel examination starting in the left lower quadrant with visualization of the sigmoid colon, proceeding proximally to the right lower quadrant to identify all the colonic segments, followed by the terminal ileum. All the remaining bowel loops were evaluated in each quadrant of the abdomen.

Statistical Analysis

Demographic data were expressed as median and range. Interobserver agreement was calculated using the Quatto method.[14] The Fleiss' *K* method is one of the tools used to test the agreement between the different examiners while being characterized by paradoxical behavior but has a limit distribution (Gauss' *z* curve). The Quatto method, instead, tests chance agreement among multiple raters based on a test statistic, χ^2. The main advantage of the test statistic χ^2 is a well-established limit distribution when either the number of subjects or the number of raters is large. Agreement is considered almost perfect if *s* ranges from 0.81 to 1, substantial if *s* ranges from 0.61 to 0.80, moderate if *s* ranges from 0.41 to 0.60, poor if it ranges from 0.40 to 0.21, and insufficient if it ranges from 0.20 to 0.01.

RESULTS

No indeterminate results were obtained for the US scan examinations. The data were of sufficient quality to allow evaluation on US interobserver agreement in all patients.

In this study, all operators agreed on the presence/absence of CD lesions and regarding distinction of absence/mild activity vs moderate/severe lesions. Using bowel US, all operators detected lesions compatible with CD with moderate/severe

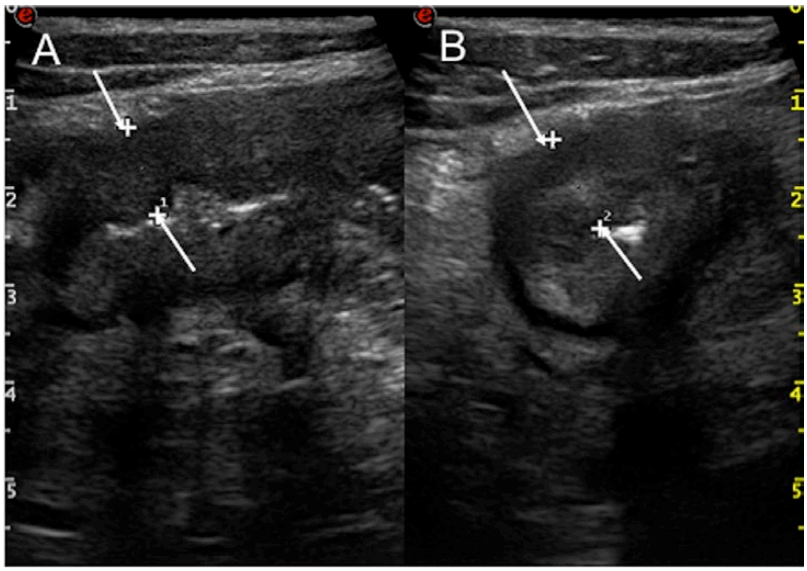

FIGURE 1. Long axis (A) and axial images (B) of the terminal ileum.

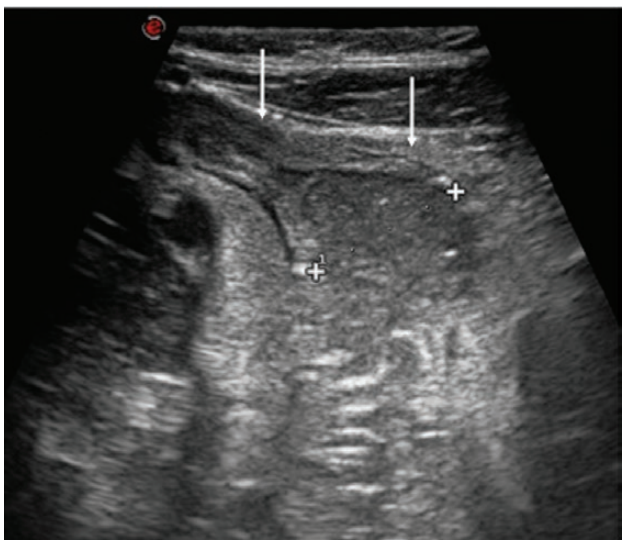

FIGURE 2. The white arrows indicate bowel wall thickness and stenosis of the terminal ileum associated with prestenotic dilation.

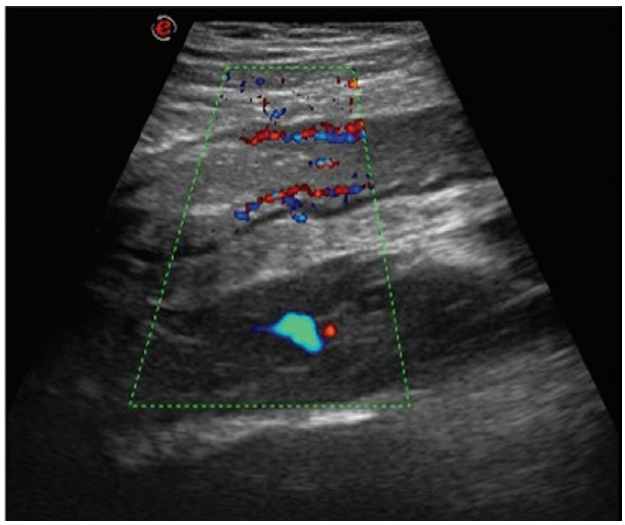

FIGURE 3. Power-Doppler ultrasound image of the affected CD segment shows moderate mural blood flow.

activity in 14 out of 15 patients. Further, in 1 patient, all the sonographers detected no lesions and no activity.

S values were moderate for bowel wall thickness (k = 0.48, *P* = n.s.), bowel wall pattern (*s* = 0.41, *P* = n.s.), vascularization (*s* = 0.52, *P* = n.s.), and presence of lymph nodes (*s* = 0.61, *P* = n.s.). Figure 4 showed agreement in detecting bowel wall thickness measurements and evaluation of bowel wall pattern (9 mm and preserved for both sonographers) in a patient with ileal CD.

Agreement was substantial for lesion location (*s* = 0.68, *P* = n.s.), fistula (*s* = 0.74, *P* = n.s.), and phlegmon (*s* = 0.78, *P* = 0.04), and it was almost perfect for abscess (*s* = 0.95, *P* = 0.02). Poor and insufficient agreements were observed for mesenteric adipose tissue alteration (*s* = 0.35, *P* = n.s.), lesion extent (*s* = 0.26, *P* = n.s.), stenosis (*s* = 0.19, *P* = n.s.), and prestenotic dilation (*s* = 0.36, *P* = n.s.).

DISCUSSION

Transabdominal US is considered a useful technique for the assessment of bowel inflammation.[9] In a systematic review conducted by Panés and colleagues, no significant differences in diagnostic accuracy among the imaging procedures (bowel US, CT, MR) were observed, and the authors concluded that because patients with IBD often need frequent re-evaluations of disease status, use of diagnostic modalities that are safe, with

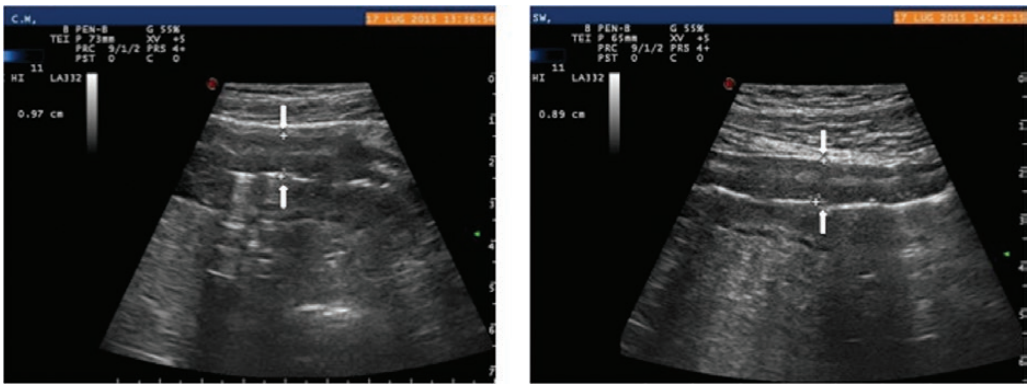

FIGURE 4. Example of agreement in detecting bowel wall thickness in a patient with ileal CD.

avoidance of ionizing radiation, is preferable. Ultrasonography is an accurate modality, readily available and inexpensive, and given repeatability, findings may help to expedite the objective and facilitate targeted therapy.

Although typical morphological imaging findings have been described in detail and reported in the literature with extensive comparisons of US with other techniques,[3–5, 9, 10] the consistency of interobserver agreement is still a matter of debate. The evaluation of the interobserver agreement is particularly relevant in bowel US, a technique whose results are strictly dependent on the operator's experience and on the possible different interpretations of US features. Preliminary results from an Italian study suggest that bowel US signs used in CD can be standardized, showing fair to good reproducibility among 6 different operators (interobserver agreement was calculated using kappa statistics for qualitative variables). In particular, BWT showed excellent reproducibility.[8] Therefore, in bowel US, it is mandatory to establish a standardization of the most frequently used US parameters.

In this international study, the majority of the US parameters used in CD patients showed moderate/substantial agreement. The development of a standardized US imaging interpretation and reporting pattern among bowel sonographers will improve comparability of US results among various centers globally, with a subsequent improvement in the quality of multicenter US studies and bowel US training with a wider dissemination of this technique. All operators agreed on the presence or absence of CD lesions and the identification of activity in all patients. Agreement in scoring of individual parameters (bowel wall thickness, bowel wall pattern, vascularization, lymph nodes) was moderate. Improvement of interobserver agreement is to be expected with enhanced operator session training, agreement on approach, and standardization of guidelines for identification of bowel lesions.

Reporting of stenosis and prestenotic dilation was not robustly reproducible between operators. This result could be related to the definition of stenosis, as this is debatable. Using bowel US, stenosis may be defined as thickened bowel walls associated with a narrowed lumen and increased lumen diameter of the proximal loop. A standardization of lumen diameter at the level of stenosis, lesion length, and prestenotic dilation diameter could help to better identify lesion compatibility with stenosis and prestenotic dilation in comparison with bowel contractions or other possible lesions. This result could be related to the short discussion during the prededicated meeting on this complication. Although the use of polyethylene glycol (PEG) solution may lead to a significantly greater accuracy of bowel US in detecting the presence and number of stenoses,[5, 6, 9] its use has not been widely adopted among the experts.

Agreement was substantial for site lesion, fistula, and phlegmon, and it was almost perfect for abscesses. Regarding the site of the lesion, high *S* values were observed both for the ileal and for the colonic tract. A very elevated level of reproducibility was reached for the presence of penetrating complications. This high level of agreement could possibly be attributed to well-defined parameters used to differentiate fistulas from phlegmon and abscesses. These results foster increased confidence in the use of bowel US in different centers in severe acute cases of CD with high clinical suspicion of septic complications (such as an abdominal mass or fever). In these settings, the use of US at the bedside during clinical assessment as a point-of-care method could be crucial in quickly resolving diagnostic questions and directing physicians to the most appropriate management.[15,16]

Use of oral and/or intravenous contrast agents and elasticity in addition to our US tool kit has led to an improvement in detecting complications in CD. Contrast-enhanced ultrasound (CEUS) can be used to quantify vascularity,[17] but it can also be used to separate vascular from avascular tissue, which is particularly useful when trying to differentiate a phlegmon from an abscess.[18] The accuracy for assessing lesions in the proximal small bowel for defining the extent of diseased ileal walls and improving stenosis detection can be significantly improved using an oral contrast agent (small intestine contrast ultrasonography).[5, 9] Elasticity imaging based on strain under deformation

and elastic modulus has been clinically applied for the evaluation of bowel lesions in CD; this technique could be a noninvasive tool to differentiate the nature of bowel strictures in vivo.[19, 20] Despite the small sample sizes of the available studies, elastography has showed extremely promising results in the field of CD. Validating the strain elastography technique in larger cohorts is needed in order to confirm its very promising results, especially as regards its prognostic value and possible role as a predictor of response to treatment in CD patients.[21] Multicenter studies are needed to evaluate all these US methods, both in characterizing CD lesions and in assessing interobserver variability.

Our study had some limitations. One is the relatively small sample size, which may lead to the underestimation of the agreement for some parameters; this would benefit from evaluation with a larger series of patients. The sample size of interobserver agreement is agnostic of previous studies or data and only depends on the number of observers and number of items rated. The second limitation could be the need to better standardize and predefine ultrasonographic parameters. Standardization of the measurement of US parameters as well as interpretation of the findings will likely further improve intra- and inter-reader variability. The lack of well-defined parameters is not a limitation of the present study as our aim was to assess the reproducibility of the technique and not its diagnostic accuracy, which has already been extensively demonstrated both in the diagnosis and monitoring of CD patients. The lack of well-defined parameters and the lack of reference standard to confirm US results are not limitations of this pilot study, as our aim was to assess the interobserver agreement of the technique and not its diagnostic accuracy, which has already been extensively assessed both in the detection and follow-up of CD patients.[15]

In conclusion, most of the US parameters used in CD patients showed moderate/substantial agreement. Good interobserver agreement is crucial in order to obtain a standardized definition of the most useful US parameters for the diagnosis and monitoring of CD patients. In fact, the development of a common US imaging interpretation pattern among bowel ultrasonographers around the world assessing patients with CD or IBD makes the development of a bowel US training program feasible in the near future and will allow widespread adoption of this technique.

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REFERENCES

1. Panes J, Bouhnik Y, Reinisch W, et al. Imaging techniques for assessment of inflammatory bowel disease: joint ECCO and ESGAR evidence-based consensus guidelines. *J Crohns Colitis*. 2013;7:556–85.
2. Calabrese E, Zorzi F, Pallone F. Ultrasound in Crohn's disease. *Curr Drug Targets*. 2012;13:1224–33.
3. Gasche C, Moser G, Turetschek K, et al. Transabdominal bowel sonography for the detection of intestinal complications in Crohn's disease. *Gut*. 1999;44:112–7.
4. Castiglione F, Mainenti PP, De Palma GD, et al. Noninvasive diagnosis of small bowel Crohn's disease: direct comparison of bowel sonography and magnetic resonance enterography. *Inflamm Bowel Dis*. 2013;19:991–8.
5. Calabrese E, Zorzi F, Onali S, et al. Accuracy of small-intestine contrast ultrasonography, compared with computed tomography enteroclysis, in characterizing lesions in patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2013;11:950–5.
6. Parente F, Greco S, Molteni M, et al. Oral contrast enhanced bowel ultrasonography in the assessment of small intestine Crohn's disease. A prospective comparison with conventional ultrasound, x ray studies, and ileocolonoscopy. *Gut*. 2004;53:1652–7.
7. Wong DD, Forbes GM, Zelesco M, et al. Crohn's disease activity: quantitative contrast-enhanced ultrasound assessment. *Abdom Imaging*. 2012;37:369–76.
8. Fraquelli M, Sarno A, Girelli C, et al. Reproducibility of bowel ultrasonography in the evaluation of Crohn's disease. *Dig Liver Dis*. 2008;40:860–6.
9. Calabrese E, Maaser C, Zorzi F, et al. Bowel ultrasonography in the management of Crohn's disease. A review with recommendations of an international panel of experts. *Inflamm Bowel Dis*. 2016;22:1168–83.
10. Maconi G, Parente F, Bollani S, et al. Abdominal ultrasound in the assessment of extent and activity of Crohn's disease: clinical significance and implication of bowel wall thickening. *Am J Gastroenterol*. 1996;91:1604–9.
11. Calabrese E, La Seta F, Buccellato A, et al. Crohn's disease: a comparative prospective study of transabdominal ultrasonography, small intestine contrast ultrasonography, and small bowel enema. *Inflamm Bowel Dis*. 2005;11:139–45.
12. Maconi G, Radice E, Greco S, et al. Bowel ultrasound in Crohn's disease. *Best Pract Res Clin Gastroenterol*. 2006;20:93–112.
13. Gomollón F, Dignass A, Annese V, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1 diagnosis and medical managment. *J Crohns Colitis*. 2017;11(1):135–49.
14. Quatto P. Un test sulla natura casuale dell'accordo tra più esaminatori. Paper presented at: Atti del 5° Congresso Nazionale della Società di Biometria. September, 10–12, 2003; Marina di Massa, Italy.
15. Panés J, Bouzas R, Chaparro M, et al. Systematic review: the use of ultrasonography, computed tomography and magnetic resonance imaging for the diagnosis, assessment of activity and abdominal complications of Crohn's disease. *Aliment Pharmacol Ther*. 2011;34:125–45.
16. Calabrese E, Zorzi F, Lolli E, et al. Positioning ultrasonography into clinical practice for the management of Crohn's disease. *Gastroenterol Hepatol (N Y)*. 2015;11:384–90.
17. Romanini L, Passamonti M, Navarria M, et al. Quantitative analysis of contrast-enhanced ultrasonography of the bowel wall can predict disease activity in inflammatory bowel disease. *Eur J Radiol*. 2014;83:1317–23.
18. Ripollés T, Martínez-Pérez MJ, Paredes JM, et al. Contrast-enhanced ultrasound in the differentiation between phlegmon and abscess in Crohn's disease and other abdominal conditions. *Eur J Radiol*. 2013;82:e525–31.
19. Baumgart DC, Müller HP, Grittner U, et al. US-based real-time elastography for the detection of fibrotic gut tissue in patients with stricturing Crohn disease. *Radiology*. 2015;275:889–99.
20. Fraquelli M, Branchi F, Cribiù FM, et al. The role of ultrasound elasticity imaging in predicting ileal fibrosis in Crohn's disease patients. *Inflamm Bowel Dis*. 2015;21:2605–12.
21. Orlando S, Fraquelli M, Colella M, et al. Ultrasound elasticity imaging predicts therapeutic outcomes of patients with Crohn's disease treated with anti-tumour necrosis factor antibodies. *J Crohns Colitis*. 2017;12(1):63–70.